DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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December 19, 2014

IMMUNODIAGNOSTIC SYSTEMS LTD.
MICK HENDERSON, RA OFFICER
10 DIDCOT WAY, BOLDON BUSINESS PARK
BOLDON, TYNE & WEAR NE35 9PD
UNITED KINGDOM

Re: K140554
Trade/Device Name: IDS-iSYS 25-Hydroxy Vitamin D^S Assay
IDS-iSYS 25-Hydroxy Vitamin D^S Control Set
Regulation Number: 21 CFR 862.1825
Regulation Name: Vitamin D test system
Regulatory Class: II
Product Code: MRG, JJX
Dated: November 10, 2014
Received: November 10, 2014

Dear Mr. Mick Henderson:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Katherine Serrano -S

For: Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
kl40554

Device Name
IDS-iSYS 25-Hydroxy Vitamin D^S
lDS-iSYS 25-Hydroxy Vitamin D^S Control Set

Indications for Use *(Describe)*
The IDS iSYS 25-Hydroxy Vitamin D^S Assay (IDS-iSYS 25OHD^S) is intended for the quantitative determination of 25-hydroxyvitamin D (25OHD) and other hydroxylated metabolites in human serum on the IDS iSYS Multi-Discipline Automated System. Results are to be used in conjunction with other clinical and laboratory data to assist the clinician in the assessment of vitamin D sufficiency in an adult population.

The IDS-iSYS 25-Hydroxy Vitamin D^S (25OHD^S) Control Set is used for quality control of the IDS-iSYS 25-Hydroxy Vitamin D^S assay on the IDS-iSYS Multi-Discipline Automated System.

Type of Use *(Select one or both, as applicable)*
[X] Prescription Use (Part 21 CFR 801 Subpart D) [ ] Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

510(k) SUMMARY

510k Number **k140554**

Introduction According to the requirements of 21CFR807.92, the following information provides sufficient detail to understand the basis for a determination of substantial equivalence.

Submitter

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Date prepared: 17, December 2014

Device Name

Proprietary names:	IDS-iSYS 25-Hydroxy Vitamin D^S IDS-iSYS 25-Hydroxy Vitamin D^S Control Set
Common names:	As above
Classification:	21CFR862.1825 Vitamin D Test System, Class II 21CFR862.1660 Quality Control Material (Assayed and Unassayed), Class I, reserved
Product Code:	MRG JJX

Predicate Device The IDS-iSYS 25-Hydroxy Vitamin D^S is substantially equivalent to other products in commercial distribution intended for similar use. We claim equivalency to the currently marketed IDS-iSYS 25-Hydroxy Vitamin D (k091849).

Device Description The IDS-iSYS 25-Hydroxy Vitamin D^S assay consists of a reagent cartridge and one set of calibrators (Calibrators A & B or CAL A & CAL B). The reagent cartridge contains multiple reagents: MPV1 (Magnetic particles coated with 25-OH D in a phosphate buffer containing methanol with sodium azide as preservative), CONJ (Anti-25-OH D sheep polyclonal antibody labelled with an acridinium ester derivative, in buffer containing bovine, sheep, rabbit and mouse proteins with sodium azide as preservative), NaOH (Sodium hydroxide solution <0.5 M), and BUF (Assay buffer containing proprietary displacing compounds, methanol, and sodium azide as preservative).

Calibrators A and B contain horse serum in a buffer matrix with two defined concentrations of 25-OH D and sodium azide as a preservative.

The IDS-iSYS 25-Hydroxy Vitamin D^S Control Set contains horse serum in a buffer matrix with three defined concentrations of 25-OH D and sodium azide as a preservative.

Indications for Use The IDS-iSYS 25-Hydroxy Vitamin D^S assay (IDS-iSYS $25OHD^s$) is intended for the quantitative determination of 25-hydroxyvitamin D (25OH D) and other hydroxylated metabolites in human serum on the IDS-iSYS Multi-Discipline Automated System. Results are to be used in conjunction with other clinical and laboratory data to assist the clinician in the assessment of vitamin D sufficiency in an adult population.
The IDS-iSYS 25-Hydroxy Vitamin D^S ($25OHD^s$) Control Set is used for quality control of the IDS-iSYS 25-Hydroxy Vitamin D^s assay on the IDS-iSYS Multi-Discipline Automated System.

Conditions for use: For in vitro diagnostic use only.
Rx Only

Comparison Tables

Similarities compared to the chosen predicate device (k091849***)***

Performance	**IDS-iSYS 25-Hydroxy Vitamin D Assay** Predicate device (k091849)	**IDS-iSYS 25-Hydroxy Vitamin D^{s}** **Candidate device**
Intended Use	Quantitative determination of 25-Hydroxy Vitamin D and other hydroxylated metabolites in human serum.	Same
Indications for use	Results are to be used in conjunction with other clinical and laboratory data to assist the clinician in the assessment of vitamin D sufficiency in an adult population.	Same
Analyte	25-Hydroxy Vitamin D (25-OH D)	Same
Calibrator matrix	Equine serum buffer matrix with two defined concentrations of 25-OH D and sodium azide as a preservative.	Same
Sample matrix (primary tube type)	Human Serum	Same
Reagent storage	2-8 °C	Same
Sample preparation (pre-treatment)	Performed on-board the analyzer	Same
Sample volume	10µL	Same
Method of detection (Test methodology)	Chemiluminescent immunoassay using magnetic-particle solid phase and acridinium label	Same
Automation	Fully automated assay	Same
Kit reagent components	Reagent cartridge (1 vial each of MPV1, CONJ, NaOH & BUF), two concentration levels of calibrators (A&B) (1 vial of each) & a mini CD	Same
Control Kit components	Three concentration levels of controls (3 vials of each) & a mini CD	Same

Calibration procedure	User-initiated 2 point calibration to adjust the batch related master curve. The system stores the calibration for the interval specified in the kit IFU.	Same
Quality Control	Requires three buffer based controls to validate the calibration	Same

Kit Controls:

Performance	**IDS-iSYS 25-Hydroxy Vitamin D Control Set** **Predicate** (k091849)	**IDS-iSYS 25-Hydroxy Vitamin D^s Control Set**
Intended Use	The quality control of the assay on the IDS-iSYS.	Same
Control matrix	Equine serum buffer matrix with three defined concentrations of 25-OH D and sodium azide as a preservative.	Same
Control Kit components	Three concentration levels of controls (3 vials of each) & a mini CD	Same
Quality Control	Requires three buffer based controls to validate the calibration	Same
Stability	After opening at 2 - 8 °C: To the expiry date On board the analyzer: 2.5 hours	Same
Reagent storage	2-8 °C	Same

Differences compared to the chosen (FDA cleared; marketed) predicate device

Performance	**Predicate device**	**Candidate device**
Kit reagent component volumes	Reagent cartridge (1 vial each): MPV1 (2.6mL), CONJ (7.1mL), NaOH (5.2mL) & BUF (26.0mL)	Reagent cartridge (1 vial each): MPV1 (2.0mL), CONJ (10.1mL), NaOH (5.2mL) & BUF (26.0mL)
Antibodies	Anti-25 OH D Sheep Polyclonal IgG	Same, but with a different source of antibody pool.
Traceability/ Standardization	Traceable to U.V. quantification.	Traceable to the isotope dilution-liquid chromatography/tandem mass spectrometry (ID-LC-/MS/MS) 25(OH)D Reference Method Procedure (RMP) which was used in assigning the target value for the VDSP samples. The ID-LC-MS/MS RMP is

		traceable to the National Institute of Standards and Technology Standard Reference Material (SRM) 2972.
Calibration interval	7 days	14 days
Range of assay	6 – 126ng/mL	7 – 125ng/mL
Sensitivity	LoB: 1.8 ng/mL LoD: 3.6 ng/mL LoQ: 6.2 ng/mL	LoB: 0.6 ng/mL LoD: 2.6 ng/mL LoQ: 7.0 ng/mL
Reference range	Non-parametric reference interval: 7.9 – 57.8ng/mL (n=150)	Non-parametric reference interval: 12.7 – 64.2ng/mL (n=275)
Assay Duration	38 minutes	36 minutes
On board the analyzer reagent stability	7 days	21 days
In use (after opening at 2-8°C) reagent stability	14 days	21 days

Performance Characteristics (if/when applicable):

1. Analytical performance:

    a. *Precision/Reproducibility:*

    A study was performed in accordance with CLSI EP5 A2 where six (6) serum samples (ranging from 12.0ng/mL to 116.5ng/mL) were assayed using three (3) lots of reagents in duplicate (n=2) twice per day for 20 days on three (3) analyzers.

Representative LOT

Sample	n	mean	Within-run		Total	
		(ng/mL)	SD	CV%	SD	CV%
Serum 1	80	13.2	0.8	6.4%	1.4	10.6%
Serum 2	80	27.2	1.5	5.4%	2.5	9.0%
Serum 3	80	38.9	2.3	5.8%	3.5	9.1%
Serum 4	80	54.5	3.2	5.8%	5.0	9.1%
Serum 5	80	77.2	4.0	5.2%	6.6	8.5%
Serum 6	80	119.9	6.1	5.1%	8.6	7.2%

b. Linearity/assay reportable range:

Linearity was evaluated based on CLSI EP-6A, "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach". In the linearity study, samples were prepared by diluting a high serum sample with a low serum sample to obtain eleven (11) concentration levels across the measuring range. One study was performed with one manufacturing batch resulting in a total of 22 concentration levels ranging from 5.8ng/mL to 152.9ng/mL. Each concentration level was assayed in duplicate, and the resulting mean concentrations were compared to predicted concentrations.

The resulting linear regression equation was $y = 0.96x + 2.1$ng/mL, $R^2 = 1.00$

The reportable range of the assay is 7-125ng/mL.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

<u>Calibrator traceability and value assignment</u>
An internal stock solution is prepared by reconstituting a vial of 25-hydroxyvitamin D_3 with ethanol and adding this to horse serum. The potency assigned to the stock solution is nominally based on the absorbance at 264nm of the ethanolic 25D solution prior to addition to the serum. A molar extinction coefficient of 18,200 is used to calculate the concentration from the absorbance value. This stock solution is used to prepare master calibrators, whose final value assignment is based on results from running the calibrators in multiple assays on multiple analyzers.

Kit calibrators are lot specific for each assay kit. Master calibrators and kit calibrators A and B are prepared gravimetrically from the stock solution or an intermediate stock solution. For value assignment, the kit calibrators are tested as unknowns in a minimum of 20 assay runs using one analyzer. Each run is calibrated using master calibrators. The values are then adjusted to ensure batch-to-batch consistency where necessary, and to facilitate the alignment to the CDC VDSP program, based on multiple correlation assays of an established patient library panel. The final assigned values obtained for the kit calibrators are verified on three additional analyzers. The values must fall within specified acceptable ranges.

The assay is traceable to the isotope dilution-liquid chromatography/tandem mass spectrometry (ID-LC-/MS/MS) 25(OH)D Reference Method Procedure (RMP) which was used in assigning the target value for the VDSP samples.

The ID-LC-MS/MS RMP is traceable to the National Institute of Standards and Technology Standard Reference Material (SRM) 2972.

Stability

As there has been no change to the kit calibrators or kit controls formulation, design or intended use, the cleared IDS-iSYS 25-Hydroxy Vitamin D product (k091849) should be referred to for the relevant performance and stability details. The calibrator and control shelf-life and open-vial stability testing protocols and acceptance criteria were described and found to be adequate. Once opened calibrators and controls are stable for up to 2.5 hours on board the analyzer. Current accelerated shelf life studies support the assigned six-month shelf life, with real-time studies on-going.

d. Detection limit:

The Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantification (LoQ) studies were performed according to CLSI EP-17A.

To establish the Limit of Blank (LoB), the zero calibrator was assayed as 10 replicates over 10 assays on 10 separate days giving a total of 100 measurements. The Limit of Blank was determined by calculating the concentration corresponding to the mean zero calibrator minus two standard deviations from the 4PL calibration curve. The LoB claim is 0.6ng/mL.

The Limit of Detection (LoD) study was performed by assaying 10 samples (native and/or diluted) with very low vitamin D concentrations (ranging from 1.9ng/mL to 8.0ng/mL) in duplicate over 12 assays spanning multiple days giving a total of 240 data points. The LoD claim is 2.6ng/mL.

The Limit of Quantification (LoQ) was determined by measuring 13 low samples (native and /or diluted) in a concentration range of 2.8 – 24.6ng/mL in duplicate over 7 individual assays spanning multiple days giving 182 data points. The LoQ claim is 7.0ng/mL and was calculated by interpolating the concentration of the analyte from the regression curve at 20% precision C.V.

e. Analytical specificity:

Cross-reactivity by adding endogenous 25(OH) vitamin D metabolite to serum samples: Endogenous 25(OH) vitamin D metabolites were spiked into vitamin D serum samples and analyzed with the IDS-iSYS 25-Hydroxy Vitamin D^S assay. The value of un-spiked sample and spike concentration were determined by LC-MS/MS 25(OH)D method. The spiked sample was measured with the IDS-iSYS 25-Hydroxy Vitamin D^S assay. The % cross-reactivity was calculated based on following equation:

$$\frac{\text{Mean conc. of spiked sample – mean conc. of unspiked sample}}{\text{Spiked concentration}} \times 100\%$$

Cross Reactant	Spike Conc. (ng/mL)	Un-spiked sample value (ng/mL)	Spiked sample value (ng/mL)	% Cross Reactivity	Mean % Cross Reactivity
$25(OH)D_3$	10.0 20.0	20.2 14.3	29.2 35.1	90% 104%	97%
$25(OH)D_2$	10.0 20.0	16.1 11.1	28.5 34.4	124% 117%	120%
$24,25(OH)_2D_3$	5.0	66.2	72.4	124%	124%

b. Cross-reactivity by adding exogenous synthetic 25(OH) vitamin D metabolite to serum samples: Exogenous synthetic 25(OH) vitamin D metabolites were spiked into vitamin D serum samples. The un-spiked and spiked samples were measured with the IDS-iSYS 25- Hydroxy Vitamin Ds assay. The % cross reactivity was calculated based on the following equation:

$$\frac{\text{Mean conc. of spiked sample – mean conc. of unspiked sample}}{\text{Spiked concentration}} \times 100\%$$

Cross Reactant	Spiked conc. (ng/mL)	Sample Native conc. (ng/mL)	% Cross reactivity	Mean % Cross reactivity
3-epi-25(OH)D3	100.0 100.0	9.4 36.4	0% 3%	1%
3-epi-25(OH)D2	100.0 100.0	8.6 33.4	0% 2%	1%
1,25-(OH)2 D3	2.0 2.0	7.1 31.2	19% -65%	-23%
1,25-(OH)2 D2	20.0 20.0	8.6 37.9	13% 5%	9%
Vitamin D3 (Cholecalciferol)	1000.0 1000.0	6.9 30.8	0% 0%	0%
Vitamin D2 (Ergocalciferol)	100.0 100.0	7.4 37.3	1% -2%	0%
Paricalcitol	100.0 100.0	8.2 33.4	0% 2.9%	0%

The following potentially interfering endogenous substances listed within the package insert do not interfere in the IDS-iSYS 25-Hydroxy Vitamin D^S assay when the concentrations presented in the following table are below the stated threshold, using a criterion of ±10% bias of the control sample to the test sample. Rheumatoid Factor was assessed using a recovery study with two 'normal' samples; the specification is based on recovery criteria of 90 - 110%. RF does not show significant interference up to 1500 IU/L tested. To evaluate potential lipid interference a natural specimen with 500mg/dL lipid concentration was obtained. A portion was delipidated and assayed along with the same unaltered specimen n=23 in the IDS-iSYS 25-Hydroxy Vitamin D^S assay.

Potentially Interfering Agent	Threshold Concentration	Sample 25OHD Concentration	n	Bias (Test vs. Control Sample)
Triglycerides	500mg/dL	50.0ng/mL & 87.9ng/mL	26 & 26	-6% & -5%
Bilirubin, conjugated	30mg/dL	18.0ng/mL & 65.7ng/mL	26 & 26	9.2% & 6.4%
Haemoglobin	40mg/dL	19.2ng/mL & 71.7ng/mL	26 & 26	-8% & -2%
Biotin	300nmol/L	17.0ng/mL & 66.2ng/mL	26 & 26	1% & -3%
HAMA	500ng/mL	18.2ng/mL & 72.8ng/mL	25 & 26	-5% & -2%
Red Blood Cells	0.2%	15.5ng/mL & 65.8ng/mL	26 & 26	-10% & -2%
Vitamin DBP	2000ng/mL	18.9ng/mL & 76.0ng/mL	24 & 26	0% & 0%

The package insert also states that the presence of haemoglobin at concentrations >40mg/dL might lead to falsely depressed values. Do not use hemolyzed samples.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed to demonstrate the accuracy of the newly aligned assay. With the aligned assay calibration parameters, 99 samples in the range of 9.0ng/mL to 98.6ng/mL, by ID-LC-MS/MS RMP, were used to assess the IDS-iSYS 25-Hydroxy Vitamin D^S assay traceability against the ID-LC-MS/MS RMP.

The relationship between the IDS-iSYS (y) and the ID-LC-MS/MS RMP (x) is described using Passing-Bablok regression & Deming regression:

Passing Bablok regression:
IDS-iSYS = 0.95 x (ID-LC-MS/MS RMP)+ 0.80ng/mL
95 % CI of the slope: 0.86 to 1.04
95 % CI of the intercept: -1.32 to 3.08ng/mL

Deming regression:
IDS-iSYS = 0.94 x (ID-LC-MS/MS RMP)+1.34ng/mL
95 % CI of the slope: 0.86 to 1.01
95 % CI of the intercept: -0.78 to 3.45ng/mL

Pearson correlation coefficient, r: 0.925

In addition, the following method comparison study was performed to characterize the comparison of the newly aligned IDS-iSYS 25-Hydroxy Vitamin D^S assay to the un-aligned IDS-iSYS 25-Hydroxy Vitamin D assay:

Method comparison studies were performed following CLSI EP9-A2. An internal method comparison study was performed with a total of 283 European-sourced serum samples tested in singlicate on the IDS-iSYS 25-Hydroxy Vitamin D^S Assay and the predicate (the IDS-iSYS 25-Hydroxy Vitamin D Assay). Samples spanned the assay range with values from 7.3 – 115.1 ng/mL (candidate values).

Passing-Bablok regression analysis was performed to produce a summary of results for each study, as shown below.

Internal Study:

Passing Bablok	y = 0.96x + 1.1ng/mL
Slope, 95% Confidence Interval	0.91 to 1.01
Intercept, 95% Confidence Interval	-0.3 to 2.3ng/mL
Correlation Coefficient, r	0.94
n	283
Range	7.3 to 115.1 ng/mL

a. Matrix comparison:

Not applicable. Only serum may be used.

3. Expected values/Reference range:

An expected values study performed according to the non-parametric method in CLSI protocol C28-A2.

Samples from 275 apparently healthy light skin and dark skin male and female adults living in the United States, aged 21 to 77 years, in geographical diverse regions of the United States to represent a broad spectrum of UV light exposure in the intended population were assayed in the IDS-iSYS 25-Hydroxy Vitamin D^S Assay.
The 95% reference interval was calculated by a non-parametric method following C28-A2. The following range was obtained:

Normal Adults 12.7 – 64.2ng/mL (n=275)

Observed sample ranges were:

	n	Observed Sample Range	Median
Non-supplemented	220	11.9 - 91.9ng/mL	31.8ng/mL
Northern US	*116*	*11.9 - 55.4ng/mL*	*29.7ng/mL*
Southern US	*104*	*14.3 - 91.9ng/mL*	*36.3ng/mL*
Supplemented	55	8.2 - 83.8ng/mL	35.3ng/mL
Overall	275	8.2 - 91.9ng/mL	32.5ng/mL

The package insert states that there is no universal agreement on the optimal concentration of 25OHD. Ranges should be based on clinical decision values that apply to both sexes of all ages rather than population based reference ranges for 25OHD.

Conclusion:

The IDS-iSYS 25-Hydroxy Vitamin D^S and IDS-iSYS 25-Hydroxy Vitamin D^S Control Set data presented and provided is complete and supports the basis for substantial equivalence to the predicate device.